The archaeon *Pyrococcus furiosus* is a strictly anaerobic microorganism that grows in shallow marine volcanic vents at temperatures near 100 °C. It obtains carbon and energy for growth by converting sugars to acetate, carbon dioxide and hydrogen gas. The organism is being used as a model system to study hydrogen metabolism and to engineer carbon and electron flow to useful products. *P. furiosus* contains three different types of hydrogenase. One is an integral membrane protein termed MBH, which is encoded by a fourteen-gene operon and functions as a simple respiratory system [1]. MBH accepts electrons from reduced ferredoxin, generated from sugar oxidation, and both reduce protons to hydrogen gas and conserve energy by generating an ion gradient, which is subsequently used for ATP synthesis. MBH has been solubilized and characterized and its properties will be discussed. The organism also contains two cytoplasmic hydrogenases that are NAD(P)-dependent and these are thought to recycle the hydrogen gas produced by MBH. Genetic techniques are being used to engineer *P. furiosus* to produce hydrogen from alternative substrates and to use hydrogen to generate alternative end products, including fuels and chemicals. In particular, strains have been constructed that use hydrogen gas to reduce carbon dioxide to a useful chemical [2] and conserve energy by oxidizing formate to produce hydrogen gas [3].

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P6.2

Flavin-based electron bifurcation: A novel mechanism of energy coupling in anaerobic microorganisms

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Flavin-based electron-bifurcation is a recently discovered mechanism of coupling endergonic to exergonic redox reactions in the cytoplasm of anaerobic bacteria and archaea. Seven electron-bifurcating enzyme complexes have been characterized to date. Their structure and function will be discussed.

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P6.3

Microbial life under extreme energy limitations: How acetogenic bacteria make a living from hydrogen and carbon dioxide

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Synthesis of acetate from carbon dioxide and molecular hydrogen via the Wood–Ljungdahl pathway is thermodynamically at the edge of life since it allows or the synthesis of only a fraction of an ATP. How the pathway is coupled with the net synthesis of ATP has been an enigma for a long time, but recently, new insights have been obtained using the anaerobic, acetogenic bacterium *Acetobacterium woodii* as a model system. This bacterium uses an ancient version of the pathway without cytochromes and quinones and couples the pathway to the generation of a transmembrane electrochemical sodium ion gradient that in turn drives ATP synthesis via a unique Na^+ F_1F_O ATP synthase that has a hybrid motor with a reduced number of Na^+ translocating sites and thus a reduced Na^+/ATP stoichiometry [1,2]. None of the enzymes of the carbon flow are membrane-bound, but one enzyme of the electron transfer pathway, the ferredoxin:NAD^+ oxidoreductase (Fno). Experiments using inverted membrane vesicles revealed that electron flow from reduced ferredoxin to NAD^+ is coupled to Na^+ export across the cytoplasmic membrane [3]. The Fno is encoded by the *rnf* genes that code for a membrane-bound electron transfer complex comprising six subunits with FeS cluster and flavins as electron carriers [4]. Inspection of the genome sequence revealed that Rnf it is the only ion pump connect to the pathway.

The Rnf complex is "fueled" with reduced ferredoxin that is assumed to have a redox potential at around −500 mV. Ferredoxin is reduced by a hydrogenase that overcomes the steep energy barrier from H_2 (E_o' $H_2/2H^+ = -414$ mV) to ferredoxin by coupling it to an exergonic reaction by electron bifurcation [5]. CO_2 reduction to formate (E_o' $H_2/2H^+ = -414$ mV) is another endergonic reaction when coupled to NADH oxidation. This energetic problem is overcome by a novel CO_2 reductase that directly uses molecular hydrogen as electron donor [6].

In summary, *A. woodii* uses a minimalistic version of the Wood–Ljungdahl pathway that is coupled to ferredoxin-reduction by electron bifurcation followed by a sodium ion translocating, ferredoxin oxidizing enzyme complex (Rnf). The Na^+ gradient drives ATP synthesis by a Na^+ F_1F_O ATP synthase with an unusual membrane-embedded rotor.

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P7 Mitochondrial Physiology

P7.1

Mitochondrial stress signaling in disease and aging

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Mitochondria are multi-faceted organelles in eukaryotic cells that stand at the nexus of energy metabolism, oxidative stress, and apoptosis. Consequently, circumstances (genetics, environmental factors, aging) that result in mitochondrial dysfunction disrupt a multitude of cellular processes that can cause human disease pathology, ranging from heart, skeletal muscle and nerve dysfunction to diabetes, blindness, and deafness. Of course, a major function of mitochondria is to generate ATP through the process of oxidative phosphorylation (OXPHOS), which also produces reactive oxygen species (ROS). Oxidative stress due to increased production of mitochondria-derived ROS, declines in cellular energy metabolism, and disruptions of apoptotic responses are some of the major downstream cellular consequences leading to the observed pathology of mitochondrial-based diseases. In addition to causing molecular damage, ROS and other forms of mitochondrial stress participate in numerous signaling pathways that regulate diverse physiological processes, including stress resistance, cell differentiation, immune system function, and apoptosis. In my talk, I will highlight studies from my laboratory that link mitochondrial stress signaling pathways to pathology, the innate immune system and regulation of lifespan.

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P7.2

Mitochondrial dynamics and inheritance in yeast

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Mitochondria are essential organelles of eukaryotic cells. They are the major sites of energy production and play important roles in programmed cell death and ageing. In many cell types, mitochondria show an amazingly dynamic behaviour. They continuously move along cytoskeletal tracks, and their membranes frequently fuse and divide. These processes are important for maintenance of mitochondrial functions, for inheritance of the organelles upon cell division, for cellular differentiation, and for programmed cell death. Budding yeast *Saccharomyces cerevisiae* is a particularly useful model organism to study these processes. Systematic screening of comprehensive yeast mutant collections revealed novel molecular components and cellular pathways required for mitochondrial fusion, division, motility, mitochondrial DNA inheritance, and respiratory activity. These large scale genetic analyses are combined with functional characterization of newly identified proteins by biochemical and imaging techniques. Our current work focuses on the molecular mechanisms contributing to mitochondrial transport, distribution, inheritance, and turn-over in yeast. The class V myosin, Myo2, was identified as the motor directing anterograde mitochondrial transport [1]. The cell cortex-associated protein, Num1, is an important factor for retention of mitochondria in the mother cell [2]. The mitochondria-ER tethering complex ERMES is crucial for mitochondrial turn-over by mitophagy [3]. The ultimate goal of our ongoing work is to obtain a comprehensive picture of the molecular processes contributing to mitochondrial inheritance in a simple eukaryotic cell.

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P7.3

Mitochondria take center stage in Alzheimer's disease

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder that affects more than 35 million people worldwide. Despite considerable progress of AD research in recent years, we still lack the means to either arrest or prevent this devastating disorder. Accumulating evidence shows that mitochondrial abnormalities elicit a cascade of pathological events that underlies neuronal degeneration in AD pathology. Studies performed in our laboratory demonstrate prominent alterations in mitochondrial structure, function, and turnover in several experimental models of AD. It was also observed that mitochondrial dysfunction is a possible bridge between AD and type 2 diabetes, a major risk factor for AD. These findings corroborate the notion that mitochondria are a promising target for drug discovery and therapeutic interventions.

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